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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,248	05/06/2002	Peter D. Davis	U 013864-1	8432

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EXAMINER

ANDERSON, REBECCA L

ART UNIT	PAPER NUMBER
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1626

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,248	DAVIS, PETER D.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____. | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Claims 1-17 are currently pending in the instant application and are rejected.

Claim Objections

Claim(s) 9, 13, 15, 16 and 17 is/are objected to for being substantial duplicates of the claims from which they depend. When two claims in an application are duplicates, or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. M.P.E.P. 706.03(k). The above mentioned claims are considered duplicate claims of the claims from which they depend because the composition claimed only contains the compound as found in the claims from which claims 9, 13, 15, 16 and 17 depend. Also, since the intended use of a product claim carries no patentable weight, these composition claims are considered duplicates of the compound claims from which they depend. This objection can be overcome by inserting --and a pharmaceutical acceptable excipient-- before the period in claims 9, 13, 15, 16 and 17.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps

required for the preparation of a composition with the cis-stilbene as found in claim 1. Therefore, claims 10 and 14 are considered indefinite for failing to include the required steps for the preparation of a composition with the cis-stilbene as found in claim 1. These claims are conclusionary in nature and provide no indication as to how the composition is made. Since claims 10 and 14 are processes for the preparation of a composition, these claims should provide the steps required in the process.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woods et al. (reference AT on form 1449).

Applicant's instant claims 1-4 are drawn towards a cis-stilbene of formula (I) (claim 1) wherein R1, R2, R3 can be methyl (claim 2), R5 is hydrogen and R4

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is alkyl or halo (claim 3). Claim 4 is drawn to the specific compound (Z) -1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethane.

Determining the scope and contents of the prior art

The prior art reference of Woods et al. discloses Combretastatin A-4, figure 1, page 705, which interacts with tubulin with resultant disruption of microtubular function. Page 709 of Woods et al. discloses that the 4'methoxy and 3'hydroxy groups of combretastatin A-4 are not essential for the interaction with tubulin. Furthermore, page 710 of Woods et al. discloses Figure 8 which shows that small alkyl groups at a position equivalent to applicant's R4 do not adversely affect activity of the compound and methoxy is not essential at this position. Page 710 discloses that the interaction with tubulin is tolerant of the replacement of the 4'-methoxy by methyl or ethyl, and also, (e) of page 710 discloses that the replacement of the 4'methoxy group of combretastatin A-4 can be replaced with small hydrophobic groups while still retaining significant activity against tubulin

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art reference and the claims at issue is that in the position equivalent to applicant's R4 substituent, the prior art reference contains a methoxy group, which is not a variable included in applicant's instant claims.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to someone of ordinary skill in the art at the time of the invention to

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prepare compounds of applicant's instant claim 1, which have vascular damaging activity, including compounds of applicants instant claim 1 wherein R1, R2, and R3 are methyl, R4 is alkyl and R5 is hydrogen when faced with combretastatin A4 in the prior art reference of Woods et al. The motivation is provided in the prior art reference by the disclosure that small alkyl groups at the 4' position do not adversely affect activity of the compound, that methoxy is not essential at the 4' position, that the interaction with tubulin is tolerant of the replacement of the 4'methoxy with methyl or ethyl and that the 4'methoxy can be replaced with small hydrophobic groups while still retaining significant activity against tubulin. The disclosure by Woods et al. that the 4'methoxy group is not necessary and that the replacement of the 4'-methoxy by a small alkyl group or small hydrophobic group would not adversely affect the activity of the compound would motivate someone of ordinary skill in the art to prepare compounds as instantly claimed by applicant in order to have more compounds which are useful for the disruption of microtubular function and for the treatment of tumors.

Claims 5-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woods et al. as applied to claims 1-4 above, and further in view of WO 92/16486 or WO 99/35150.

Applicants instant claims 5-19 are drawn towards prodrugs of the compound of formula (I), specifically phosphate esters of the compound of formula (I), (claims 5-8, 11 and 12), compositions of the compound of formula (I) (claims 9, 13 and 15-17) and processes for the preparation of compositions of the compound of formula (I) (claims 10 and 14).

Determining the scope and contents of the prior art

WO/92/16486 discloses compounds which have greater aqueous solubility than Combretastatin A4 and exhibit greater stability, which are prodrugs such as the compound of formula (I) (page 2) wherein Y is a phosphate or a phosphate derivative, the prodrug of the phosphate derivative is particularly preferred (page 3). These compounds can be dissolved in a phosphate buffered saline (page 20) for the preparation of a pharmaceutical formulation of the compound.

WO 99/35150 discloses combretastatin A4 prodrugs, of which phosphate salts are the most stable and suitable (page 6). Page 7 discloses phosphate ester prodrugs which are water soluble. These compounds can be added to a sterile vehicle such as water to be administered as a pharmaceutical composition (page 36).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art of WO 92/16486 and the instant claims is that the prior art reference discloses phosphate ester prodrugs of Combretastatin A-4, wherein the position equivalent to applicant's R4 is a methoxy group and the prior art reference discloses pharmaceutical formulations and their methods of preparation for Combretastatin A-4, wherein position 4' is substituted with a methoxy.

The difference between the prior art of WO 99/35150 and the instant claims is that the prior art reference discloses phosphate ester prodrugs of Combretastatin A-4, wherein the position equivalent to applicant's R4 is a methoxy group and the prior art reference discloses pharmaceutical formulations

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and their methods of preparation for Combretastatin A-4, wherein position 4' is substituted with a methoxy.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to someone of ordinary skill in the art to prepare phosphate ester prodrugs of the compound as found in applicants instant claim 1 and to prepare pharmaceutical compositions when faced with the prior art reference of Woods et al. and one of WO 92/16486 or WO 99/35150 since Woods et al. discloses that the 4'methoxy of Combretastatin A-4 can be replaced by a small alkyl group or a small hydrophobic group without causing an adverse reaction in activity and Wo 92/16486 or WO 99/35150 disclose the phosphate ester prodrugs of Combretastatin A4 and disclose that these phosphate esters have improved aqueous solubility and characteristics for use as a prodrug in pharmaceutical formulations. One of ordinary skill in the art would be motivated to prepare prodrugs of the formula as instantly claimed by applicant and to prepare pharmaceutical compositions by the prior art references to prepare other useful compounds which interact with tubulin and are useful in the treatment of cancer.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (703) 605-1157. Mrs. Anderson can normally be reached Monday through Friday 7:00AM to 3:30PM.

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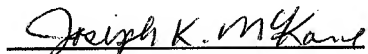
If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (703) 308-4537.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4242, (703) 305-3592, and (703) 305-3014.



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